D2

22. (Once amended) The method according to Claim 1, wherein:

a) the proportion of the cells of the preproduction batch forming said first part ranges from 80% to 90%, and

b) the proportion of the cells of the preproduction batch forming said second part ranges from 10% to 20%.

REMARKS

I. Status of the Claims

Claims 1, 2, and 7-26 are pending. Claims 1, 2, and 22 have been amended without prejudice to pursuing canceled subject matter, if any, in a continuing application, and without disclaimer of any subject matter, to more particularly point out and distinctly claim the subject matter Applicant regards as his invention. Specifically, claim 1 now recites that the preproduction batch of section a) is divided into "a first part and a second part." Support for this amendment can be found, among other places, in the specification at page 2, lines 4-7. Claim 1 has also been amended to recite that the method is discontinuous. Support for this amendment can be found throughout the application and claims as originally filed, and in the specification at page 2, line 3. Claims 2 and 22 have been amended to reflect the changes made to claim 1.

One of ordinary skill in the art will know to construe the "first part" and "second part" language in the intended manner. While the cells of the preproduction batch are divided into two parts, the skilled artisan will know that a portion of the cells may also be diverted for other purposes, such as for safety analysis. This knowledge comes from the knowledge common to those of ordinary skill in the art, and also from the

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specification at page 4, lines 26-33. Moreover, such division into two parts does not require a collection of 100% of the cells of the preproduction batch. As is known in the art, some cells may be left behind, for example, in a transferring step, and some cells may not be viable. *See, e.g.,* Example 5, specification at pages 8-9. Finally, the preproduction batch is used to create one or several production batches, and one or several subsequent preproduction batches. *See* sections c) and d) of claim 1 (thrice amended). Thus, one may not divide the cells of a preproduction batch into a nominal third part, for example, and escape the literal scope of Applicant's claims.

II. New Matter Objection and Rejection

The Preliminary Amendment filed on July 16, 2002, has been objected to under 35 U.S.C. § 132 as allegedly introducing new matter into this application. Office Action dated September 20, 2002, at page 2. Specifically, "the added material which is not supported by the original disclosure is as follows: 'b) dividing the cells of the preproduction batch [into] at least two separate batch[es].' " *Id.* Further, on page 5 of the Office Action, claims 1-2 and 7-26 have been rejected under 35 U.S.C. § 112, ¶ 1, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicant, at the time the application was filed, had possession of the claimed invention. Specifically, the same language objected to under 35 U.S.C. § 132 has been rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking written description support in the specification. *See id.* at page 5. Applicant respectfully disagrees with this allegation of new matter.

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Without acquiescing to the charge that new matter has been added to the application, Applicant has amended claims 1, 2, and 22 to recite language finding clear, literal support in the specification. Claim 1 now recites "dividing the cells of the preproduction batch into a first part and a second part." Support for this language can be found, among other places, in the specification at page 2, lines 4-7, where Applicant describes "part of the cells of the preproduction batch" being used for one purpose, and "the remaining part of the cells of the preproduction batch" being used for a second purpose.

Since none of the rejected claims as amended recite the language quoted by the Examiner, both of these rejections should be withdrawn.

III. Claim Rejections under 35 U.S.C. § 102

A. *Griffiths et al.*

Claims 1-2, 9-22, and 26 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Griffiths et al.* (Methods in Molecular Biology (1997) 75:59-76). Office Action at page 2. Applicant respectfully traverses this rejection, for at least two reasons.

First, *Griffiths et al.* may not be prior art to the present application. Applicant encloses a search report showing a catalogue date of January 14, 1999, for the volume in which *Griffiths et al.* appears. *See* Biomedical Information Service search report, enclosed. According to this report, 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS SECOND EDITION (Jeffrey W. Pollard & John M. Walker eds., 1997), did not appear on the shelves of the library of Des Moines University until January 14,

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1999, long after Applicant's priority date (December 24, 1997) and international filing date (December 17, 1998). The M.P.E.P. tells us that *Griffiths et al.* is not prior art unless the Examiner can show an earlier publication date:

> A publication disseminated by mail is not prior art until it is received by at least one member of the public. Thus, a magazine or technical journal is effective as of its date of publication (date when first person receives it) not the date it was mailed or sent to the publisher.

M.P.E.P. § 2128.02 (*citing In re Schlittler,* 234 F.2d 882, 110 U.S.P.Q. (BNA) 304 (C.C.P.A. 1956).). In case the Examiner can show an earlier publication date, and in the interest of advancing prosecution, Applicant also addresses the merits of the rejection.

Second, the disclosure of *Griffiths et al.* fails to describe the claimed invention. *Griffiths et al.* teaches how to operate various systems available for scaling up cell cultures. In general, a small number of cells is placed in a bioreactor of some kind, and allowed to grow into a larger number of cells. *Griffiths et al.* describes the advantages, shortcomings, and considerations related to each bioreactor system.

Griffiths et al., however, does not anticipate Applicant's claimed invention. M.P.E.P. § 2131 articulates the standard for anticipation: " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' " (*quoting Verdegaal Bros., Inc. v. Union Oil Co. of Cal.,* 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).).

Applicant's amended claim 1 recites:

> b) dividing the cells of the preproduction batch into a first part and a second part,
> c) employing said first part for the preparation of at least one production batch for the production of at least one biological,

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d) employing said second part as a seed for the preparation of at least one subsequent preproduction batch.

A thorough review of *Griffiths et al.* reveals no discussion of dividing cells into two parts in the manner claimed. When it comes to growing more cells, the cells in *Griffiths et al.* are always used as a single "part" and are never diverted for more than one purpose. *Griffiths et al.* does remove "a small sample" to test for cell viability during the course of culturing. *See Griffiths et al.* at page 63, lines 7-10. The taking of this small sample during culturing, however, does not represent dividing a preproduction batch into two parts for preparing "at least one production batch" and "at least one subsequent preproduction batch." It appears that *Griffiths et al.* tests, and then discards, cells taken in the "small sample." *See id.*

Moreover, the Examiner misreads the disclosure of *Griffiths et al.* For example, the Examiner alleges: "*Griffiths et al.* taught that during the second step of the scale-up culture, the cell density/unit volume increase 10-100 time, in another word, at the begging [beginning] of the culture, the cell population is only 10% of the final volume of the culture (pp. 60, lines 2-5)." Office Action at page 3. In the cited passage, *Griffiths et al.* is not teaching a second step of scaling up a culture. Instead, *Griffiths et al.* describes two approaches to scale-up: "The first [approach] is volumetric - a simple increase in volume while retaining the same cell density or process intensity. The second method is to increase the cell density/unit vol 10-100-fold by means of medium perfusion techniques." *Griffiths et al.* at page 60, lines 3-6.

The two approaches of *Griffiths et al.* underscore the novelty of Applicant's claimed method. *Griffiths'* first approach appears in *Wiktor et al.* (U.S. Patent No. 4,664,912), mentioned in Applicant's specification on page 1. *Wiktor et al.* describes an

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expansion of preproduction batches from a 1 liter biogenerator up to a 1000 liter biogenerator. *Wiktor et al.* at col. 2, lines 58-69. Only after all preproduction batches have been prepared is the production batch cultured: "the inoculation by the virus [is] effected in this *last* passage." *Id.* at lines 68-69 (emphasis added). The second approach to scaling-up appears in several places in *Griffiths et al.*, where medium perfusion techniques and equipment are discussed. *See, for example, Griffiths et al.* at page 60, lines 5-13.

Applicant has invented a third approach: the skilled artisan cultures subsequent preproduction batches and production batches from the *same* preproduction batch. This allows, potentially, the skilled artisan to culture subsequent preproduction batches and production batches at the same time. Using this approach, a vaccine manufacturer, for example, can rapidly produce vaccine without waiting for all preproduction batches to reach full maturity. *See* specification at page 3, line 35 to page 4, line 2; *contrast with Wiktor et al.* at col. 2, lines 68-69. A description of this third approach cannot be derived from the disclosure of *Griffiths et al.*

Applicant respectfully contends that the standard for finding anticipation is not met by the disclosure of *Griffiths et al.*, so the rejection should be withdrawn.

The Examiner also asserts that Applicant has failed to comply with 37 C.F.R. § 1.111(c), allegedly because Applicant has not clearly pointed out the patentable novelty which he thinks "the claims present in view of the state of the art disclosed by the references cited or the objections made." Office Action at pages 3-4. In response, Applicant points out that the cited documents do not describe, among other things, sections b), c), and d) of Applicant's claim 1. "Further, [Applicant does] not show how

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the amendments avoid such references or objections." *Id.* at page 4. While maintaining that the cited documents and rejections do not necessarily apply to the pending claims, Applicant directs the Examiner's attention to the remarks appearing throughout this Amendment.

B. *Davis et al.*

Claims 1-2, 9, 11-14, 22, and 24-25 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by *Davis et al.* (Methods in Molecular Biology (1997) 75:77-89). Office Action at page 5. After characterizing the disclosure of *Davis et al.,* the Examiner asserts inherent anticipation of Applicant's claimed method. Applicant respectfully disagrees with this rejection.

Since *Davis et al.* appears in the same volume as *Griffiths et al.,* it may not be effective as prior art until January 14, 1999, after the international filing date of the present application. *See* Biomedical Information Service search report, enclosed. Unless a publication date earlier than Applicants' priority date can be shown, *Davis et al.* cannot be applied against the pending claims. *See* M.P.E.P. § 2128.02.

Davis et al. teaches a method of performing hollow-fiber cell culture. Details of setting up, characterizing, inoculating, culturing for up to six months, and shutting down such a culture are given. The Examiner points to *Davis'* "step 10" on page 87 to support the assertion that cultured cells can be preserved for future use. Office Action at page 5. Step 10 states: "10. If a post-production cell bank is to be made, culture the cells to obtain maximum viability and freeze according to standard procedures." This step describes saving a portion of a production batch, after production is complete. In fact,

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this is the final step in a process the authors call "Removal of Cells from the Hollow-Fiber Cartridge at the *End of a Run*." *Davis et al.* at page 86 (emphasis added). All production has ceased, and cells are gathered merely for characterization. Notably, this step does not suggest any division of a batch of cells before production begins.

Nowhere does *Davis et al.* expressly describe Applicant's claimed method. Pending claim 1 recites:

> dividing the cells of the preproduction batch into a first part and a second part, . . . employing said first part for the preparation of at least one production batch . . . [and] employing said second part as a seed for the preparation of at least one subsequent preproduction batch.

Davis et al. shows no description of such dividing. Also, *Davis et al.* shows no dual use of cells from a preproduction batch. *See, for example, Davis et al.* at pages 83-85 (*describing* inoculation, growth phase, and production phase of culture).

Moreover, *Davis et al.* does not provide inherent disclosure of Applicant's claimed method. " 'To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' " M.P.E.P. § 2112 (*quoting In re Robertson,* 169 F.3d 743, 745, 49 U.S.P.Q.2d (BNA) 1949, 1950-51 (Fed. Cir. 1999) (further internal quotations omitted).). This two-fold test has not been addressed in the rejection. Accordingly, the rejection over *Davis et al.* based on inherent disclosure has not been established. Moreover, the disclosure of *Davis et al.* does not meet the two-fold test for inherency. Applicant's claimed "dividing" and "employing" of the parts of the preproduction batch, for example, are not "necessarily present" in *Davis et al.;* nor would the skilled artisan recognize that subject matter as being necessarily present in the disclosure of *Davis et al.*

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Given the lack of anticipating disclosure by *Davis et al.,* Applicant respectfully requests that this rejection be withdrawn.

IV. Rejection under 35 U.S.C. § 103

Claims 1-2 and 7-22 have been rejected under 35 U.S.C. § 103(a) over *Griffiths et al.* and *Pollard* (Methods in Molecular Biology (1997) 75:1-11). Office Action at page 4. Applicant contends that this rejection is improper, first, since these documents may not be prior art, and second, because the combination of these documents does not teach or suggest the claimed invention.

Griffiths et al. and *Pollard* may not be effective as prior art until January 14, 1999, after the international filing date of the present application. *See* Biomedical Information Service search report, enclosed. *Pollard* appears in the same volume as *Griffiths et al.,* and so shares the same publication date. Unless an earlier publication date is shown, these two documents cannot be applied against the pending claims. *See* M.P.E.P. § 2128.02.

A rejection under 35 U.S.C. § 103(a) requires, among other things, that the alleged prior art references, when combined, "must teach or suggest all the claim limitations." M.P.E.P. § 2143.

Applicant's claim 1, as amended, recites a method comprising:

> a) culturing cells to form a preproduction batch, b) dividing the cells of the preproduction batch into a first part and a second part, c) employing said first part for the preparation of at least one production batch for the production of at least one biological, d) employing said second part as a seed for the preparation of at least one subsequent preproduction batch . . . .

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As discussed above, *Griffiths et al.* fails to describe dividing preproduction batches into two parts and employing the two parts for at least one production batch and as a seed for at least one subsequent preproduction batch. *Pollard* does not cure this failure. *Pollard* teaches methods for establishing and maintaining cell cultures and methods for freezing the cells (items 3.1-3.3). *Pollard* does not, however, teach or suggest dividing preproduction batches into separate parts and employing the separate parts as claimed. Thus, the applied references, when combined, fail to teach or suggest all the limitations set forth in claim 1. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

The Examiner reads too much into the cited documents. The Examiner states that "splitting the cell culture in certain ration according to the demanded usage, . . . are all taught by Griffiths." Office Action at page 4. Splitting cells in certain ratios are not taught by *Griffiths et al.* Instead, *Griffiths et al.* seems to be concerned with merely growing the greatest number of viable cells possible, and no adjustments to split ratios because of demanded usage appear in *Griffiths et al.*

The Examiner reveals the logic of the rejection at the bottom of page 4 of the Office Action:

> Although the claims are amended to dividing cells into at least two batch, one batch is used for production and another batch is seeded for subsequent preparation, the modification of the splitting cells in different ratios is generally recognized as being within the level of the ordinary skill in the art, because it has been held that where general conditions of a claim are disclosed in the prior art, discovering the workable ranges involves only routine skill in the art.

(citations omitted). This logic rests on a mistaken premise. Applicant's cells are not merely divided into a split ratio that falls within the range of ratios disclosed in the cited

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documents. Applicant divides the cells of the preproduction batch into two separate parts, one part for a production batch or batches and a second part to seed a subsequent preproduction batch or batches. This division is not taught or suggested in the cited documents, regardless of any split ratios which may be disclosed.

At least because sections b), c), and d) of Applicant's sole independent claim 1 are not taught or suggested by the combined teachings of the cited documents, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant respectfully requests entry of these amendments, reconsideration of this application, and timely allowance of the pending claims.

Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 20, 2002

By: Charles E. Van Horn #40266
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Enclosures:
Appendix
Biomedical Information Service search report.

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